Reply To Examiner's Remarks

Claims 1-20 and 43-48, as amended, are presented for consideration.

The Examiner declines to accept an executed Terminal Disclaimer for the application, submitted on or around 30 September 2003, asserting that the person who signed the Terminal Disclaimer has failed to state his capacity to sign for the Assignee and has not been established as being authorized to act on behalf of the Assignee. A new Terminal Disclaimer, executed by the Applicant's patent representative of record, is submitted herewith, with apologies to the Examiner for the lapse in execution.

The Examiner rejects claims 1-20 and 43-48, as amended in the 30 September 2003 response, under 35 U.S.C. 112, first paragraph, as containing subject matter that was not adequately described in the patent application. The Examiner asserts that

"On page 7 of the specification, Applicant has disclosed measuring blood velocity. However, Applicant has not disclosed measuring vascular size associated with a target site with any of the sensors claimed in amended claims 1 and 9. It is noted that claims 1 and 9 are enabled to only use interstitial fluid pressure sensors to determine a characteristic of a margin of a target. See page 6 of the specification. In addition, claims 1 and 9, as amended, are enabled to determine vascular density only by measuring pO2, See p. 7 of the Specification."

The relevant portions of the specification, at pages 6-9, are set forth in the following nine paragraphs, for reference.

"The margins of certain tumors may have certain characteristics that differ from the corresponding characteristics for the core or interior of the tumor. For example, the increased interstitial fluid pressure in the core of a tumor drops sharply to that of a normal region near an edge of a tumor, as reported by P. Vaupel, in "Vascularization, blood flow, oxygenation, tissue pH, and bioenergetic status of human breast cancer", Oxygen Transport to Tissue, Plenum Press, New York, vol. 18 (1997), pp. 143-154, and discussed in greater detail in the following. Comparison of these characteristics for the margin(s) and for the core, using

selected scanning or imaging techniques, may help distinguish between the presence and absence of certain kinds of tumors. The size of a margin or transition region may also indicate presence of a non-normal target site. For example, a margin size for a well developed tumor is typically about 2.7 mm.

"An estimate can be made of blood flow velocity adjacent to or within the target site using a sensor that estimates blood flow using a Doppler velocity sensor or similar indirect estimating procedures. For a normal breast, a breast with a benign tumor and a breast with a malignant tumor, measured mean blood flow values are 311 ± 157 flux units, 482 ± 209 flux units and 711 ± 280 flux units, respectively. Thus, larger than normal blood flow velocity appears to indicate presence of a benign or malignant tumor.

"Where measured vascular density for a target site is higher, by a multiplicative factor of 2-10 or higher, than a normal range of vascular density (e.g., 2-3 per mm^2) for that site, this condition often indicates the presence of a malignant tumor. Comparison of measured vascular size with vascular size range for a normal target site (e.g., 0.2 mm) can indicate presence of a class of non-normal medical conditions (benign or malignant), especially if the measured size is at least 200 percent higher than the normal range of sizes.

"P. Vaupel, op cit, notes that growth of an avascular, three-dimensional aggregate of tumor cells is self-limiting. The establishment of progressive expansion of malignant tumors is possible only if supply and drainage are initiated through blood flow through exchange vessels in a tumor bed, using pre-existing normal host blood vessels and using newly-formed tumor vessels arising from neovascularization. Angiogenesis, the formation of new capillaries from an existing vascular network, appears to be essential for tumor growth and metastasis, and some angiogenesis parameters (pO2, vascular count, vessel morphology, etc.) can also be used for prognosis. Greater vascular density may be associated with longer patient survival, although some other studies reach an opposite conclusion. A growing tumor is unable to form its own lymphatic system and must rely on other sources for blood, nutrients, oxygen, etc. Bulk flow of free fluid in interstitial

spaces appears to be much higher in a tumorous region than in a normal region: 15 percent of normal convective plasma flow for breast cancer regions versus 0.5-1 percent of normal convective plasma flow for a normal region. These increased interstitial fluid pressures drop sharply near the edge of a tumor

"Interstitial fluid pressure (IFP) is a measure of a balance of fluid entering a target site and fluid exiting from the target site. Only an invasive breast tumor has a consistently higher IFP value (15-32 mm Hg) than does a normal or healthy breast (-0.4 to +4 mm Hg), where an IFP measurement needle tip is located within the tumor region. The results reported in the preceding paragraph by Vaupel, op cit, are also relevant here.

"Comparison of oxygen tension pO2 (or PPO) for a selected region adjacent to or within the target site with corresponding values for a normal target site can provide an indication of whether or not a particular class of medical conditions is present. Vaupel, Kallinowski and Okunieff, in "Blood Flow, Oxygen and Nutrient Supply, and Metabolic Microenvironment of Human Tumors; A Review", [citation] report on a study of change of pO2 in cervical mucosa with progress of cervical cancer. In a normal, non-cancerous cervix, the the pO2 median value is 36 mm Hg. For stages 0, 1 and 2 of cervical cancer, the pO2 median value drops to 20 mm Hg, to 13 mm Hg and to 5 mm Hg, respectively. The measured pO2 value appears to move to lower and lower values as cancer progresses, as compared to a normal or healthy range for the cervix. A non-metastasizing breast tumor ($pO2 \approx$ 20 mm Hg) has a larger mean pO2 value than does a metastasizing breast tumor ($pO2 \approx 7.5$ mm Hg). Based on other measurements reported, a tumor growing in association with an organ appears to require at least 50 percent more oxygen than a normal organ, and this may be manifested by a much smaller pO2 value where a tumor is present.

"Results reported by Vaupel, op cit, on oxygen consumption in a breast cancer tumor (3-10 μl/gm/min) versus oxygen consumption in a normal region (3-6 μl/gm/min) are consistent with these results. Hypoxia is present in many tumorous regions. Vaupel found pO2 values of 0-2.5 mm Hg for breast tumors and

pO2 values of at least 12.5 mm Hg for normal regions. A bimodal pO2 distribution is often manifested, indicating presence of normal and hypoxic regions side by side.

For a tumorous target site versus a normal target site, the following characteristics are discussed: (1) margin size or transition size; (2) blood flow velocity adjacent to the target site; (3) interstitial fluid pressure (IFP) at margin; (4) vascular density; (5) vascular size; (6) interstitial fluid pressure within target site; and (7) pO2 within or adjacent to target site. Two references are further cited and discussed in connection with these characteristics that provide additional information on, and connections between, the characteristics: P. Vaupel, op cit, and Vaupel, Kallinowski and Okunieff, op cit.

This material appears to provide adequate relationships for the following system components, as recited in claims 1 and 9: a ninth sensor that measures a selected characteristic [e.g.,, margin size, IFP or blood flow velocity] of a margin of the target site; and a tenth sensor that measures at least one of vascular size and vascular density associated with the target site.

This material discloses that measurement of vascular density is included among the different measurements that can be made to distinguish between normal, benign and malignant medical conditions. The Applicant believes this discussion in the specification adequately discloses measurement of vascular density, for purposes of recitation of this measurement in the claims. Claims 1 and 9 are amended herein to limit recitation of the actions of the ninth and tenth sensors to what is explicitly recited in the text and the two cited references. The Applicant believes that claims 1 and 9, as amended, are adequately described in the specification and in the two cited references.

The Examiner rejects claims 1-20 and 43-48 under 35 U.S.C. 102(e) as anticipated by the disclosures in U.S. Patent No. 6,135,965, issued to Tumer et al. The Tumer et al patent discloses method and apparatus for spectroscopic detection of cervical pre-cancer, using fluorescence spectroscopy measurements that are classified using a trained radial basis neural network. This process distinguishes

pre-cancerous tissue from normal tissue, using an optical system with a sequence of selected wavelengths of radiation. The Tumer et al patent does not disclose or suggest measurement of any of the three margin characteristic or measurement of vascular density or measurement of vascular size, as recited in amended claims 1 and 9.. Because of these differences, the Applicant believes that claims 1 and 9, as amended, are allowable over the disclosures in the Tumer et al patent.

The applicant requests that the Examiner pass the application, including claims 1-20 and 43-48, as amended, to issue as a U.S. patent.

Respectfully Submitted,

John Schipper

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